Depression after myocardial infarction

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Chapter Nine

IX

Inspired by the influential study by Frasure-Smith et al (*Journal of the American Medical Association 1993*), in which it was described that depression following myocardial infarction (MI) was associated with a worse cardiac prognosis, many studies have tried to replicate this finding. Most of these studies were able to confirm this observation, however several studies failed to find an association between post-MI depression and impaired cardiovascular prognosis. Nevertheless, depression is considered to be an independent risk factor for post-MI prognosis. Indeed, some research groups share the opinion that depression in the aftermath of MI is *causally* related to new cardiac events. Given the previous conflicting results, we set out to investigate the association between post-MI depression and cardiovascular prognosis in a meta-analysis. We selected and pooled prospective studies in which the effects of depression (within 3 months post-MI) on cardiovascular mortality and events within 2 years post-MI was investigated. It was shown in **chapter 2** that post-MI depression was associated with a 2-2.5 fold increased risk of cardiovascular mortality or cardiovascular events (e.g. recurrent MI, dotter procedures, etcetera). These results support the assumption that post-MI depression is related to a worse cardiac prognosis. However, to satisfy the criteria of causal inference, effective treatment of post-MI depression should lead to a better cardiovascular outcome of depressive MI patients. Therefore, we designed the Myocardial INfarction and Depression - Intervention Trial (MIND-IT) (**chapter 3**). This large randomised controlled study investigated the influence of antidepressive treatment for depression following MI on cardiac prognosis. Other objectives were the investigation of antidepressive treatment for post-MI depression on a) quality of life b) depression. The study was sponsored by the Netherlands Heart Foundation. To answer the research questions, MI patients admitted to 10 hospitals, scattered nationwide, were screened for depressive symptoms and disorders. Of 2177 MI patients, screened in the first year post-MI, 17% fulfilled the criteria (ICD-10) of depressive disorder at some timepoint in that year. This percentage is comparable to results from other research groups. Patients who scored positive for depressive disorder during a standardised psychiatric interview differed from patients who remained free from depression on several characteristics. Important predictors of post-MI depression were a) young age and b) poor left ventricular function. In combination with the results of a depression questionnaire during hospitalisation, it appeared to be possible to identify MI patients with a high risk for subsequent development of depression. The predictor model **(chapter 6)** may be of value in rehabilitation and work-resumption programs of patients who suffered from MI.

In MIND-IT, MI patients with post-MI depression were randomised to Intervention (n=208) or Care as Usual (n=122). Patients randomised to Intervention were offered antidepressive treatment, which consisted of treatment with mirtazapine, citalopram or another treatment (which was at the discretion of the treating psychiatrist). The kind of

treatment realized was not essential for the investigation of the primary objective based on the assumption that optimal antidepressive treatment was provided in the Intervention arm, compared with almost negligible antidepressive treatment in the CAU-arm. No treatment was offered by MIND-IT investigators in the CAU-arm. The final results of the MIND-IT study showed that antidepressive treatment did not improve the cardiac prognosis of MI patients with depression compared to CAU patients (**chapter 3**). However, for a clear interpretation of the study results, it need to be stressed that due to the absence of a difference in depression outcome between the randomisation arms, it remains undecided whether *effective* treatment of post-MI depression can increase event-free survival.

Two other conclusions can be drawn from the MIND-IT study. Firstly, based on long-term follow up of depression outcome of CAU patients, we showed that most of the depressive patients (~70%) were recovered at 18 months post-MI. From these data it may be clear that most of the depressive episodes after MI (but not all!) should be considered as a temporary mood disorder in response to a life-threatening event. Secondly, pharmacological treatment of post-MI depression did not result in a better cardiac outcome. This may be of importance, since recent studies showed that certain antidepressants (i.e. the specific serotonin re-uptake inhibitors, SSRIs), in contrast to other psychiatric treatment modalities, may have protective properties in ischaemic heart disaese, which could be due to its effects on blood platelet activation. It must be realized that the antidepressants used within the MIND-IT study, belonged mostly to another pharmacological class than these SSRIs. Therefore, more research is warranted to investigate the effects of SSRIs on the cardiovascular system.

One of these initiatives is presented in **chapter 5**. It was shown that one of the SSRIs, sertraline, showed marked vasodilatory effects in rat aorta and human IMAs (Internal Mammary Arteries). Sertraline also elicited vasodilatation in coronary arteries during perfusion of rat hearts. These hemodynamic effects may be an additional explanation for the putative beneficial effects in myocardial ischemia and infarction. In the same chapter, the results of another biological study were described. Our objective was to investigate the association between the autonomic nervous system, using parameters of Heart Rate Variability (HRV), and depression in post-MI patients. Patients with depression were characterized by decreased HRV compared to the patients without depression, independent of other clinical variables. This observation supports the concept that one of the mechanisms underlying the detrimental effect of depression on post-MI prognosis may be that depression adds to the autonomic derangement post-MI.

Based on MIND-IT data, it was shown that a relationship was found between left ven-

tricular ejection fraction (LVEF) and post-MI depressive disorder, i.e. a lower LVEF was associated with a higher rate of depression in the year post-MI. The association persisted after adjustment for demographics, risk factors for coronary artery disease, co-morbidity, heart failure and baseline depression-scores. In addition, the severity of depressive symptoms was significantly related to the severity of LV-dysfunction **chapter 4**.
Given the observed association between depression and LVEF, a closer look at the possible harmful ingredients of post-MI depression is opportune. After factor analysis of thousands of MIND-IT questionnaires, 3 dimensions (i.e. somatic/affective, cognitive/affective and appetitive symptoms) were related to prospective cardiovascular mortality and cardiac-related readmissions with a mean follow up duration of 2.5 years. Somatic/affective symptoms of post-MI depression were prospectively associated with cardiac prognosis. Cognitive/affective symptoms of depression were only marginally related to prognosis.

In chapter 7, the present status of post-MI depression is discussed. Future research questions are formulated. A comparison is made with the situation in 1993 when Frasure-Smith *et al* call attention to the harmful of post-MI depression. Although it is clear that depression has detrimental effects on the quality of life of post-MI patients, it remains to be elucidated whether depression is causally related to post-MI cardiac prognosis and whether effective treatment for this disorder can result in an increased cardiac event-free survival. Irrespective of the effects of post-MI depression on cardiovascular prognosis, clinicians need to be open minded for psychic complaints.